

**REMARKS**

Claims 1-21, 23, 24, 26-28, 30-33, 35, 37, 40-44, and 46-93 are pending. Claims 7-11, 17-20, 32, 41-44, and 46-93 are withdrawn. Claim 12 is canceled herein. Therefore, claims 1-6, 13-16, 21, 23, 24, 26-28, 30, 31, 33, 35, 37, and 40, are under consideration. Claim 1 has been amended herein to recite “healthy control.” Support for the amendment to Claim 1 can be found throughout the specification and at least on page 34, lines 11-22 and in original Claim 12 where the term control is defined. Claim 15 has been amended to recite “wherein greater than 2.5 times more multinucleated cells in the sample from the subject than in the sample from the healthy control indicates erosive arthritis in the subject.” Claim 33 has been amended to recite “wherein greater than 2.5 times more OCP in the PBMC of the subject than in a sample from a control subject without erosive arthritis indicates the presence of erosive arthritis in the subject.” Support for the amendment to Claims 15 and 33, can be found at least on page 99, lines 1-6 and in Figure 3, Figure 1, and Figure 26. Applicants believe that these amendments do not constitute new matter nor raise new issues. Moreover, Applicants submit that these amendments were not made for reasons of patentability as the claims were clear as previously written.

**35 U.S.C. § 112, second paragraph**

Claims 1-6, 12-16, 21, 23, 24, 26-28, 30, 31, and 33 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. In particular the Examiner alleges that claim 1 is vague and indefinite for the recitation “relative to a control subject.” The Examiner asserts that the recitation “fails to define what is encompassed in the term “control subject.” Applicants respectfully disagree and point out the specification specifically defines what is meant by a control in paragraph 84 located on page 34, lines 8-22. Specifically, the specification defines a control as:

any individual that has not been diagnosed as having the disorder or condition being assayed. The terms “normal control” and “healthy control” likewise mean a sample (e.g., cells, serum, tissue) taken from a source (e.g., subject, control subject, cell line) that does not have the condition or disorder being assayed and therefore may be used to determine the baseline for the condition or disorder being measured. Normal control and healthy control may also refer to samples taken from a source but not subject to a modification or stimulus that would result in the activation of differentiation of the sample.

Thus, a control is, in fact, a healthy or normal control and would need no further definition. Moreover, Applicants respectfully note that one of skill in the art would clearly understand what is encompassed by the term control. Nevertheless, in an effort to move prosecution of the application forward, Applicants have amended claim 1. Specifically, Applicants have amended claim 1 to recite “relative to a healthy control subject.” Applicants note that as this amendment is completely within the definition of control as defined in the specification, the additional term to refer to a “health control subject” is in no way further limiting as the claim always had this meaning and is now somewhat redundant. Applicants believe that the Examiner’s rejection has been addressed by Applicants’ amendments and respectfully request that the rejection be withdrawn.

Regarding the rejection of Claim 33 as allegedly also being indefinite, Applicants believe that the rejection was made in error and note that the Examiner asserts that “claim 33 fails to make clear as to whether the control should be a normal (healthy) control or an abnormal control.” Applicants respectfully point out that Claim 33 recites that the control subject is a “control subject **without erosive arthritis**.” Clearly, if the control subject is without erosive arthritis, the control subject is a healthy normal control. Thus, as presently amended, one of skill in the art would understand that the only reasonable interpretation of the control subject that falls within the scope of the claim is a control subject without erosive arthritis (i.e., a healthy control). Applicants believe that this rejection has been overcome and respectfully request its withdrawal.

The Examiner has rejected claims 15 and 33 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for the recitation of “more.” In particular, the Examiner asserts that “the term ‘more’ is not defined by the claim [and] the specification does not provide a standard for ascertaining the requisite degree, and one of skill in the art would not be reasonably apprised of the scope of the invention.” The Examiner further states that the term “more is a relative term which lacks a comparative basis for defining its metes and bounds, albeit recited to be comparative to a control subject.” Applicants maintain that the recitation “more” would be understood by those of skill in the art and remind the Examiner that “the fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite.” *Seattle Box Co., v Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). In fact, as stated in MPEP 2173, the primary purpose of the clarity requirement

under 35 U.S.C 112, second paragraph, “is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent.” Applicants note that both claims 15 and 33 provide a comparative basis for determining the presence of an increase in cells. Nevertheless, in an effort to advance prosecution, Applicants have amended claims 15 and 33 to recite “greater than 2.5 times more.” Applicants note that as amended Claims 15 and 33 provide a very specific basis for determination of whether enough of an increase in multinucleated or OCPs was observed to diagnose a subject with or determining the presence of erosive arthritis. Applicants believe this rejection has been overcome in light of Applicants amendments and respectfully request its withdrawal.

Claim 33 is rejected under 35 U.S.C. § 112, second paragraph as allegedly lacking antecedent basis for the term “presence of disease,” in the claim. Applicants respectfully point out that Claim 33 is an independent claim which is directed to “[a] method of determining the presence of an erosive arthritis in a subject...wherein more OCP...indicates the presence of erosive arthritis in the subject.” Applicants respectfully point out that every use of a term in the close of the claim has a preceding use in the preamble preceded by the article “a” with the exception of the term “presence.” Regarding the term presence, Applicants respectfully note that the use of the article “the” before presence in the preamble is not something that requires prior introduction. An entity is either present or it is not. It is an inherent feature and thus requires no antecedent introduction. If one is claiming a method of determining whether something exists, it would be impossible to do so and not make reference to the presence or absence of the thing being detected. Applicants believe this rejection to be misplaced and respectfully request its withdrawal.

Applicants believe these rejections have been overcome and respectfully request their withdrawal.

### **Double Patenting**

Claims 1-3, 12-16, 21-26, and 33-36 have been objected to under 37 C.F.R. § 1.78(b) as allegedly being a substantial duplicate of and provisionally rejected to under 35 U.S.C. § 101 as allegedly constituting double patenting in view of claims 1-3, 11-13, 15, 16, 21-26, and 33-36 of U.S. Application No. 10/548,389. Applicants acknowledge the rejection and will formally

respond to the provisional double patenting rejection in the appropriate application once claims are found to be allowable necessitating the removal of the provisional status of the rejection.

**35 U.S.C. § 102(a)**

Claims 1-6, 12, 14, 21, 23, 24, 28, 30, 35, 40, and 49 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Hirayama et al. (2002) *Rheumatology* 41:1232-1239. Applicants again respectfully point out that claim 49 has been withdrawn from consideration and therefore not under examination. Additionally, Claim 12 has been canceled herein; therefore, the rejection is moot with respect to this claim.

Applicants respectfully point out that in order for a reference to anticipate a claim, it must teach each and every limitation of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claim 1, and the claims depending therefrom, is drawn to diagnosing “erosive arthritis” by “correlating the number of OCP in the subject with the presence of erosive arthritis, wherein an increase in the number of OCP in the subject relative to a control subject indicates the presence of erosive arthritis.” Applicants respectfully point out that Hirayama et al. does not disclose let alone teach correlating erosive arthritis with an increase in the number of OCP relative to a control without erosive arthritis as claimed herein. In fact, nowhere in Hirayama specifically states any association of the number of OCP with erosive arthritis. Accordingly Hirayama fails to teach each and every limitation of the claim.

The Examiner contends that Hirayama et al. teach that “RA patients show bone erosion (erosive arthritis) on radiograph which is manifested as lower bone mineral density (p. 1232, col. 1).” Applicants first note that there is no mention anywhere on page 1232 of bone erosion in RA patients being shown on radiographs. In fact, nowhere in Hirayama et al. are Applicants able to find any evidence of a radiograph being used let alone one that shows erosive arthritis. The only reference to lower bone mineral density in RA patients is made in the background of the paper as a reference to another paper, but no mention is made of how the low density was determined. Moreover, the Examiner makes the medically incorrect assumption that the presence of lower bone density equates with bone loss and thus indicates the presence of erosive arthritis. In fact,

not all osteopenia (low bone density) results in bone loss so the presence of low bone density does not necessarily indicate the patients in those references had bone loss. Additionally, not all bone erosion is indicative of erosive arthritis. Erosive arthritis is a particular form of arthritis with a particular type of bone loss. That is, patients with erosive arthritis display focal erosions affecting the immediate subchondral bone and bone at the joint margins (see page 110, lines 20-25 of the present application where a few characteristic features of erosive arthritis are discussed). The presence of focal erosions can not be determined via a mere determination of osteopenia. Because each and every limitation of the claim is not taught by Hirayama, the reference can not anticipate the claim. Applicants respectfully request that the rejection be withdrawn with respect to these claims and their dependencies.

Regarding claims 28 and 30, Applicants remind the Examiner that as these claims depend from Claim 26 which is not rejected over Hirayama et al. Because claims 28 and 30 import all the limitations of Claim 26 and Claim 26 is free of the art, Claims 28 and 30 must also be free of the art. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Regarding claims 35 and 40, Applicants respectfully point out that claim 35, and claim 40 which depends therefore, recites a method of determining whether a subject has erosive arthritis comprising among other things “probing for three or more surface markers of mononuclear OCP, wherein the surface markers are selected from the group consisting of CD14, CD11b, CD51/CD61, RANK, CCR1, CCR4, VCAM (CD106), VLA-4 (CD49d), CD11a, MHC Class II, B7.1, B7.2, CD40, c-fms and CD16.” As noted above, for a claim to be anticipated, each and every limitation must be taught by the art. Importantly, nowhere in Hirayama et al. is a determination of erosive arthritis made by probing for three or markers from the list enumerated in claim 35. In fact, because Hirayama et al. does not provide any mechanism to determine if the patients displayed therein have erosive arthritis, it would be impossible to establish that any markers therein were indicative of erosive arthritis. Stated another way, Hirayama et al. is not enabling for any teaching relating to erosive arthritis let alone the particular teachings claimed herein. Accordingly Hirayama fails to teach each and every limitation of the claim. Because each and every limitation of the claim is not taught by Hirayama, the reference can not anticipate the claim. Applicants believe that in light of the amendments made to claim 35 this rejection has been overcome and respectfully request its withdrawal.

Claims 1-5, 12, 14, 21, 23, 24, 26-28 and 35 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Jevon et al. (2003) *Scand J. Rheumatol.* 32:95-100. Applicants respectfully point out that claim 12 has been canceled; therefore, the rejection is moot with respect to this claim. Applicants respectfully traverse the rejection. Applicants respectfully point out that in order for a reference to anticipate the claim, it must teach each and every limitation of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants note that claims 1, 26, and 35 recite that the subject has “erosive arthritis.” Applicants respectfully point out that Jevon et al. does not disclose let alone teach erosive arthritis as claimed herein. Specifically, Jevon et al. does not teach erosive arthritis. The Examiner continues to make the scientific mistake of equating “reduced bone mass” with erosive arthritis. However, reduced bone mass is not the equivalent of erosive arthritis which is a particular condition marked by “focal erosions affecting the immediate subchondral bone and bone at the joint margins” (see page 110, lines 20-25 of the present application where a few characteristic features of erosive arthritis are discussed). Jevon et al. conduct no test nor make any showing that discloses or discusses erosive arthritis. Because each and every limitation of the claim is not taught by Jevon, the reference can not anticipate the claim. Applicants believe that in light of the amendments made to claims 1 and 26, this rejection has been overcome. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

**35 U.S.C. § 103**

Claims 13, 15, 16, 29, 31, 33, and 37 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Hirayama et al. in view of Li et al. (2002) *J. Bone and Mineral Research*. JBMR Program and Abstracts 2002. Applicants respectfully point out that claims 29, 36, and 45 have been canceled; therefore, the rejection is moot with respect to these claims. Applicants respectfully traverse the rejection. In the recent *KSR Int’l Co. v. Teleflex, Inc.* ruling, the Supreme Court has reaffirmed the *Graham* factors for determination of obvious under 35 U.S.C. 103(a). *KSR Int’l Co. v. Teleflex, Inc. (KSR)*, No 04-1350 (U.S. Apr. 30, 2007). The three factual inquiries under *Graham* require examination of: (1) the scope and content of the prior art;

(2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere (Graham)*, 383 U.S. 1, 17-18, 149 USPQ 459, 467 (1966). Additionally, the court in *Graham* noted a fourth consideration for the determination of obviousness would be any objective evidence of secondary considerations such as unexpected results, unmet need in the art, and commercial success.

Applicants respectfully point out that in order to render a claim obvious all the limitations must be disclosed by the combination of references as well as the general knowledge in the art. As noted above, Hirayama does not teach anything related to erosive arthritis let alone a method of diagnosing a subject with erosive arthritis comprising a step of correlating the number of OCP with the presence of erosive arthritis. Accordingly, the Examiner must rely on Li to teach that an increased number of OCP relative to a control without erosive arthritis indicates the presence of erosive arthritis. As noted by the Examiner, Li et al merely teaches that TNFa is an osteoclastogenic factor and is important along with RANK/RANKL in the process of OCP differentiation. Li et al does not teach the number of OCP is increased in subjects with erosive arthritis. Moreover, Applicants note that neither Hirayama nor Li teach a method of determining the presence of erosive arthritis comprising among other things probing with three or more markers from the list enumerated in claim 35. Thus alone or in combination, the art fails to teach all the limitations of the claims. For this reason alone the claims are not obvious.

Furthermore, Applicants respectfully point out that on page 1237, column 1, paragraph 1 of Hirayama, the authors note that “As assessed by TRAP+ MNC formation in PBMC cultures, RA patients did **NOT** have more circulating osteoclast precursors in the monocyte fraction.” [emphasis added] This is the exact opposite of the finding herein. As noted in KSR, “When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious.” KSR at 1395. Because Hirayama specifically teaches away from the claimed invention, it can not render the claimed methods obvious. The Examiner has provided no reasoned argument why this teaching in Hirayama is being ignored. Applicants respectfully remind the Examiner that the art must be considered in its entirety. For this reason alone this rejection has been overcome. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No payment is believed to be due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted by EFS-WEB on the date indicated below.

/J. Gibson Lanier/

August 28, 2009

J. Gibson Lanier

Date